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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/036,444	MORETTA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47,64-68 and 74-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *47,64-68 and 84* is/are allowed.

6)☒ Claim(s) *74-78,80,81,85-89 and 91-96* is/are rejected.

7)☒ Claim(s) *79,82,83 and 90* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 47, 64-68 and 74-96 are pending.

2. In view of the amendment filed 8/13/04, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 74-78, 80-81, 85-89, and 91-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method for stimulation of cytotoxicity by NK cells comprising contacting said NK cells with an antibody such as polyclonal antibody, monoclonal antibody, humanized antibody and antibody of human origin that specifically binds to a polypeptide comprising SEQ ID NO: 2, or an antibody that binds specifically to a peptide *consisting* of SEQ ID NO: 7, **does not** reasonably provide enablement for (1) a method for stimulation of cytotoxicity by NK cells as set forth in claims 74-78 and 81 comprising contacting NK cells with any antibody such as polyclonal, monoclonal, humanized mouse monoclonal, antibody of human origin that specifically binds to a polypeptide "comprising" the amino acid sequence of SEQ ID NO: 7, and (2) a method of binding NK cells to any antibody comprising contacting said NK cells with any antibody such as polyclonal, monoclonal, humanized, antibody of human origin, or immunoreactive fragment thereof or labeled antibody or labeled immunoreactive fragment thereof that specifically binds to any "immunogenic fragment thereof of" NKp30 polypeptide (SEQ ID NO: 2). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient

to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method for stimulation of cytotoxicity by NK cells comprising contacting said NK cells with an antibody such as polyclonal antibody AZ20, monoclonal antibody such as A76 and Z25, humanized antibody and antibody of human origin that specifically binds to a NK receptor polypeptide comprising SEQ ID NO: 2, or an antibody that binds specifically to a peptide which is an extracellular domain of said NK receptor consisting of SEQ ID NO: 4 or an immunogenic peptide consisting of SEQ ID NO: 7 derived from amino acid position 20 to position 33 of SEQ ID NO: 2 (page 31, line 15 of specification). The specification further discloses that the use of AZ20 antibody binding fragment F(ab')2 did not induce triggering of cytolytic activity, indicating that NKp30 stimulation requires efficient crosslinking mediated by the FcγR on target cells (See page 38, line 1-5, in particular).

The specification does not teach how to make and use any antibody or binding fragment thereof mentioned above that binds to any polypeptide "comprising" the amino acid sequence of SEQ ID NO: 4, any polypeptide "comprising" the amino acid sequence of SEQ ID NO: 7, and any "immunogenic fragment" of SEQ ID NO: 2. The term "comprising" is open-ended. It expands the fragment of SEQ ID NO: 4 to include additional amino acids at either or both ends of SEQ ID NO: 4. Likewise, it expands the fragment of SEQ ID NO: 7 to include additional amino acids at either or both ends of SEQ ID NO: 7. There is insufficient guidance as to the binding specificity of the claimed antibody or labeled antibody that binds to any polypeptide comprising the amino acid sequence of SEQ ID NO: 4 or SEQ ID NO: 7, much less about the undisclosed antibody would stimulate cytotoxicity fo NK cell. Given the lack of guidance as to the structure of the peptide, there is insufficient working example demonstrating that the antibody would bind specifically to SEQ ID NO: 4 or SEQ ID NO: 7, in turn, binding is equivalent to stimulating NK cells cytotoxicity for the claimed method.

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

It is well known in the art at the time the invention was made that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994,

page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.

Abaza *et al*, of record, teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Without the specific amino acid residues of the polypeptide "comprising" the amino acid sequence of SE QID NO: 7 or the "immunogenic fragment thereof", it is unpredictable which antibody generated from an undisclosed polypeptide or fragment thereof will have the same binding specificity as an antibody generated from the peptide consisting of SEQ ID NO: 7, in turn, useful for a method of stimulating NK cytolytic activity or binding NK cells.

Since the binding specificity of *all* antibody and structure of the amino acid sequence of a polypeptide comprising the amino acid sequence of SEQ ID NO: 4 and SEQ ID NO: 7, and any immunogenic fragment thereof of SEQ ID NO: 2 are not enabled, it follows that the method of making and using the antibody for the claimed method of stimulating cytotoxicity of NK cells are not enabled. It also follows that the method of binding NK cells using any antibody or reactive fragment that binds to any immunogenic fragment thereof of SEQ ID NO: 2 coupled to a label such as fluorescent label, or attached to a solid support is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 8/13/04 have been fully considered but are not found persuasive.

Applicants' position is that the specification, as tiled, enables the breadth of the presently claimed invention. As the Patent Office is aware, the quantity of experimentation can be "considerable", "tedious", "laborious" and "time-consuming" as long as the experiments are

"merely routine". See Ex parte Jackson, 2 17 U.S.P.Q. 804, 807 (B.P.A.I. 1982) ("[t]he test (of enablement) is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine."; Exparte Erlich 3 U.S.P.Q.Zd 101 1 (B.P.A.I. 1982) (observing that although a method might be "tedious and laborious," such experimentation is nevertheless "routine" defining "routine" experiments as those which use known methods in combination with the variables taught in the patent to achieve the expected, specific, patented result). In the case of the instant invention, Applicants submit that the specification provides explicit teachings regarding methods of making antibodies that stimulate the cytotoxicity of NK cells, methods of assaying NK cells to identify such antibodies, (substitute specification at pages 27-32) as well the criteria by which stimulatory antibodies according to the subject invention are identified (see substitute specification at pages 9-10, 27-32, Example 1, and Example 2 (pages 48-50).

It is the examiner's position that it is not routine to make antibody that binds to all undisclosed polypeptide. Further, antibody binding does not equal to stimulating NK activity. SEQ ID NO: 4 and SEQ ID NO: 7 are peptide fragment from the full-length amino acid sequence comprising SEQ ID NO: 2. As evident by the teachings of Kuby et al, immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Abaza *et al*, of record, teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Given the lack of guidance as to the structure of the polypeptide comprising SEQ ID NO: 4 or SEQ ID NO: 7, it is unpredictable which other antibody would bind specifically to SEQ ID NO: 4 and 7 by immunizing any polypeptide comprising SEQ ID NO: 4 or SEQ ID NO: 7. There is insufficient biochemical or structural information that enables the skilled artisan to make and use the antibody for the claimed method as broadly claimed without the amino acid sequence of the polypeptide. There is insufficient working example demonstrating that any antibody produced by immunizing any polypeptide would bind specifically to SEQ ID NO: 2, 4 or 7, much less stimulating NK activity.

5. Claims 74-78, 80-81, 85-89, and 91-96 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) all antibody such as polyclonal, monoclonal, humanized, or human antibody that binds to any polypeptide "comprising" the amino acid sequence of SEQ ID NO: 4 or SEQ ID NO: 7 for the claimed method of stimulation of cytotoxicity of NK cells, and (2) all antibody such as polyclonal, monoclonal, humanized, or human antibody that binds to any "immunogenic fragment thereof" of SEQ ID NO: 2 for the claimed method of binding NK cells to any antibody.

The specification discloses only one immunogenic fragment of SEQ ID NO: 2 consisting of the amino acid sequence of SEQ ID NO: 7. The specification discloses a method for stimulation of cytotoxicity by NK cells comprising contacting said NK cells with an antibody that specifically binds to the NKp30 receptor polypeptide comprising SEQ ID NO: 2, or a peptide which is an extracellular domain of said NK receptor consisting of the amino acid sequence of SEQ ID NO: 4, or a peptide consisting of SEQ ID NO: 7. The specification further discloses antibody that binds to a polypeptide consisting of SEQ ID NO: 5 (transmembrane region) and a polypeptide consisting of SEQ ID NO: 6 (intracellular region) for detection assay.

With the exception of the specific polypeptide and peptides mentioned above to which the antibody binds for the claimed methods, there is inadequate written description about the structure associated with function of any polypeptide "comprising" the amino acid sequence of SEQ ID NO: 4 or SEQ ID NO: 7 and any "immunogenic fragment" of SEQ ID NO: 2 because the term "comprising" is open-ended. It expands the peptide of SEQ ID NO: 4 and SEQ ID NO: 7 to include additional amino acids at either or both ends. There is inadequate written description about which undisclosed amino acids to added, much less about the binding specificity of the antibody for the claimed methods.

Other than the specific polypeptides to which the antibody binds for the claimed method, the specification's description of exemplary antibody from one NKp30 polypeptide and two NKp30 polypeptide fragment consisting of SEQ ID NO: 4 and 7 do not appear to describe a representative number of species within the genus. In addition, neither the exemplary embodiments nor the specification's general method appears to describe the structural features i.e., amino acid sequence that are common to the genus of "immunogenic fragment thereof". One

of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 8/13/04 have been fully considered but are not found persuasive. Applicants submit that the scope of such a claim is supported by the as-filed specification i.e., having adequate written description with respect to the claimed method and enabling the practice of the claimed invention) since it is taught that antibodies that specifically bind to SEQ ID NO: 2 (the full length human NK p30 polypeptide), 4 (the extracellular domain of human NK p30), or 7 (an antigenic fragment of human NK p30). Indeed, polyclonal antibodies that were generated against the polypeptide of SEQ ID NO: 7 conjugated to KLH (an exemplary polypeptide comprising SEQ ID NO: 7 (see substitute specification page 33, lines 5-201) are able to bind to and/or stimulate the cytotoxic activity of the NK cells (see Example 1). As the Patent Office will note, polyclonal antibodies were generated against SEQ ID NO: 7 which was conjugated to KLH specifically bound to NKp30 polypeptides. Furthermore, these polyclonal antibodies were able to immunoprecipitate polyclonal NK cell populations (see, for example, Figure 9 and pages 32-33 and 44-45 of the substitute specification). It is further submitted that adequate written description exists for polypeptides comprising SEQ ID NO: 4 or 7 in that the "function" associated with these polypeptides is the binding of antibodies generated against these peptide fragments of SEQ ID NO: 2 or against the full-length sequence of SEQ ID NO: 2. Indeed, it is respectfully submitted that one skilled in the art would reasonably expect antibodies directed against SEQ ID NOS: 2, 4, or 7 to specifically bind to the NKp30 polypeptide and stimulate the cytotoxic activity of NK cells given the evidence provided in the as-filed application in Example 1 (namely that such antibodies immunoreact with the NKp30 polypeptide that is expressed on the surface of NK cells (see, for example Figures 3-7 and Figures 9A-B and the descriptions thereof at pages 22-27).

It is the examiner's position that antibody binding does not equal to stimulating NK activity. Further, SEQ ID NO: 4 and SEQ ID NO: 7 are peptide fragment derived from the full-length amino acid sequence comprising SEQ ID NO: 2.

The specification discloses only a method for stimulation of cytotoxicity by NK cells comprising contacting said NK cells with an antibody that specifically binds to the NKp30 receptor polypeptide comprising SEQ ID NO: 2, or a peptide which is an extracellular domain of said NK receptor consisting of SEQ ID NO: 4, or an immunogenic peptide consisting of SEQ ID NO: 7. The specification further discloses antibody that binds to a polypeptide consisting of SEQ ID NO: 5 (transmembrane region) and a polypeptide consisting of SEQ ID NO: 6 (intracellular region) for detection assay.

With the exception of the specific polypeptide and peptides mentioned above to which the antibody binds for the claimed methods, there is inadequate written description about the structure associated with function of any polypeptide "comprising" the amino acid sequence of SEQ ID NO: 4 or SEQ ID NO: 7 and any "immunogenic fragment" of SEQ ID NO: 2 because the term "comprising" is open-ended. It expands the peptide of SEQ ID NO: 4 and SEQ ID NO: 7 to include additional amino acids at either or both ends. There is inadequate written description about which undisclosed amino acids to added, much less about the binding specificity of the antibody for the claimed methods.

Other than the specific polypeptides to which the antibody binds for the claimed method, the specification's description of exemplary antibody from one NKp30 polypeptide and two NKp30 polypeptide fragment consisting of SEQ ID NO: 4 and 7 do not appear to describe a representative number of species within the genus. In addition, neither the exemplary embodiments nor the specification's general method appears to describe the structural features that are common to the genus of "immunogenic fragment thereof". One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

6. Claim 94 is rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "paramagnetic microsphere" and "dense particle" in Claim 94 represents a departure from the specification and the claims as originally filed. The passage cited by applicant,

particularly example 3, does not have support for "paramagnetic microsphere" and "dense particles".

Applicants' arguments filed 8/13/04 have been fully considered but are not found persuasive. Applicants submit that these claims are supported in the originally filed specification at, for example, page 10, about line 20 or pages 50-51 (Example 3) of the substitute specification.

However, the passage cited by applicant, particularly example 3, does not have support for "*paramagnetic* microsphere" and "*dense* particles". The specification on page 51 of substitute specification discloses "matrix consists of a solid phase coated with a saturating amount of anti-NKp30 antibody, such as hollow fibers, dextran particles or magnetic particles".

7. The following new grounds of rejections are necessitated by the amendment filed 8/13/04.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 85-87, 91-92 and 95-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biassoni et al (Accession No AJ223153 Sept 1, 1999; PTO 892) in view of Harlow et al (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 92-94, pages 116-117 and 359-366), and Campbell *et al* (in Monoclonal Antibody Technology, 1984, Elsevier Science Publisher, New York, NY, page 1-32; PTO 892).

Biassoni et al teach a human NK-A1 activating NK receptor comprising the amino acid sequence 100% identical to the claimed SEQ ID NO: 2 (See enclosed sequence, in particular). The reference sequence is expressed on human activated NK cells (see entitle, in particular).

The invention in claim 85 differs from the teachings of the reference only in that a method of binding NK cells to antibody comprising contacting NK cells with an antibody that specifically binds to a polypeptide comprising the amino acid sequence of SEQ ID NO: 2.

The invention in claim 86 differs from the teachings of the reference only in that the method wherein the antibody is a polyclonal antibody.

The invention in claim 86 differs from the teachings of the reference only in that the method wherein the antibody is a monoclonal antibody.

The invention in claim 91 differs from the teachings of the reference only in that the method wherein the antibody is coupled to a label.

The invention in claim 92 differs from the teachings of the reference only in that the method wherein the antibody is coupled to a fluorescent label.

Harlow *et al* teach various binding assays such as binding any cells to any antibody of interest (see page 364-367, in particular) and methods of making polyclonal and monoclonal antibody that binds to any polypeptide of interested (See page 92-94, page 116-117 in particular). Harlow *et al* also teach a method of labeling any antibody with various labels such as enzyme, fluorescent, radioisotope (See page 395, in particular) for various binding assays. The advantage of polyclonal antibodies is that it has excellent signal strength, good specificity and some background whereas monoclonal antibody has fair to good signal strength, excellent specificity and unlimited supply (see page 366, in particular). The advantages of enzyme labeling are longer shelf life, and higher sensitivity (See page 398, in particular). Harlow *et al* teach that the advantages of monoclonal antibody are their binding specificity, their homogeneity and their ability to be produced in unlimited quantities by hybridoma (See page 141, last full paragraph, in particular).

Campbell *et al* teach that "it is customary now for any group working on a macromolecule to both clone the gene encoding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)" for further basic research and diagnostic uses (See page17, and 29, section Basic Research, in particular). Campbell *et al* further teach conventional antiserum which is polyclonal antibody (See page 4, comparison of monoclonal antibodies and conventional antiserum, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to substitute the polypeptide to which the antibody binds in the binding assay as taught by Harlow et al for the polypeptide comprising SEQ ID NO: 2 that expressed on activated NK cells as taught by Biassoni et al for further characterization as taught by Campbell *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to make monoclonal or polyclonal antibodies to the claimed polypeptide based on the fact that it is a conventional practice in the art to do so for further study such as basic research, characterization and identification of a polypeptide as taught by Campbell *et al.* Biassoni et al teach the reference polypeptide is a human NK-A1 activating NK receptor that expressed on human activated NK cells (see entitle, in particular). One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to do binding assay using polyclonal or monoclonal antibody because Harlow *et al* teach that the advantage of polyclonal antibodies is that it has excellent signal strength, good specificity and some background whereas monoclonal antibody has fair to good signal strength, excellent specificity and unlimited supply (see page 366, in particular). Harlow *et al* teach that the advantages of enzyme labeling are longer shelf life, and higher sensitivity (See page 322, in particular). Claim 96 is included in this rejection because the antibody taught by Harlow and Campbell using the polypeptide as taught by Biassoni et al would crosslink NKp30 of SEQ ID NO: 2 because the polypeptide taught by Biassoni is 100% identical to the claimed NKp30 of SEQ ID NO: 2.

11. Claims 88-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biassoni et al (Accession No AJ223153 Sept 1, 1999; PTO 892) in view of Harlow et al (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 92-94, pages 116-117 and 359-366), Campbell *et al* (in Monoclonal Antibody Technology, 1984, Elsevier Science Publisher, New York, NY, page 1-32; PTO 892) as applied to claims 85-87, 91-92 and 95-96 and further in view of US Pat No. 5,530,101, filed Dec 1990; PTO 892).

The combined teachings of Biassoni et al, Harlow et al and Campbell et al have been discussed supra.

The claimed invention in claim 88 differs from the teachings of the combined references only in that the antibody is a humanized mouse monoclonal antibody.

The claimed invention in claim 89 differs from the teachings of the combined references only in that the antibody is an antibody of human origin.

The '101 patent teaches a method of producing humanized antibodies (See column 19 line 27-30; column 38, line 54, in particular). The '101 patent further teaches that humanized immunoglobulins (antibodies) or human antibody will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen (See column 3, lines 32-37, in particular) and will be particularly useful in treating human disorders susceptible to monoclonal antibody therapy (See column 2, line 54-56, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to produce humanized mouse monoclonal antibody or isolate antibody from human origin that is specific for NK-A1 activating NK receptor as taught by Biassoni and Harlow et al or Campbell. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with an expectation of success to produce humanized antibodies or antibody with human origin because the '101 patent teaches that humanized immunoglobulins (antibodies) will be substantially non-immunogenic in humans and retain substantially the same affinity as the donor immunoglobulin to the antigen (See column 3, lines 32-37, in particular) and will be particularly useful in treating human disorders susceptible to monoclonal antibody therapy (See column 2, line 54-56, in particular).

12. Claims 93-94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biassoni et al (Accession No AJ223153 Sept 1, 1999; PTO 892) in view of Harlow et al (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 92-94, pages 116-117 and 359-366), Campbell *et al* (in Monoclonal Antibody Technology, 1984, Elsevier Science Publisher, New York, NY, page 1-32; PTO 892) as applied to claims 85-87, 91-92 and 95-96 and further in view of Ellison et al (J Immunological Methods 186: 233-243; 1995; PTO 892).

The combined teachings of Biassoni et al, Harlow et al and Campbell et al have been discussed supra.

The claimed invention in claim 93 differs from the teachings of the combined references only in that the antibody is attached to a solid support.

The claimed invention in claim 94 differs from the teachings of the combined references only in that the antibody is attached to a solid support is a paramagnetic microspheres.

Ellison et al teach a method of binding NK cells to antibody such as anti-NK1.1 antibody (see entire document, abstract, in particular). The reference method comprises binding the reference antibody such as anti-NK1.1 antibody to a solid support such as protein A column (see page 235, col. 1, in particular) or micro magnetic beads (See page 241, col. 2, in particular). The advantage of the reference method is that it has minimally interference with the ability of the isolated NK cells to function as cytotoxic effector cells since the diameter of the magnetic microsphere is only 100-150 nm diameter and does not significantly alter the optical properties of positively labeled cells and the cells can therefore be used in subsequent flow cytometry studies (see 241, col. 2, in particular). The reference method is useful for purifying large numbers of NK cells for flow cytometric and functional analysis (see abstract, in particular).

Therefore, it would be been obvious to one having ordinary skill in the art at the time the invention was made to attached the antibody that binds specifically to SEQ ID NO: 2 as taught by Biassoni et al, Harlow et al and Campbell et al to the solid support such as paramagnetic beads as taught by Ellison et al for a method of binding NK cells to the antibody. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated with a reasonable expectation of success to do this because the solid support such as magnetic microsphere that is only 100-150 nm diameter does not significantly alter the optical properties of positively labeled cells and the cells can therefore be used in subsequent flow cytometry studies (see 241, col. 2, in particular). The reference method is useful for purifying large numbers of NK cells for flow cytometric and functional analysis (see abstract, in particular). Biassoni et al teach the reference polypeptide is a human NK-A1 activating NK receptor that expressed on human activated NK cells (see entitle, in particular). Campbell et al teach it is a conventional practice in the art to make antibody to a polypeptide for further study such as basic research, characterization and identification of a polypeptide.

13. Claims 47, 64-68 and 84 are allowed.

14. Claims 79, 82-83 and 90 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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November 23, 2004

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